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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/730,790 | 12/05/2000 | Mark H. Tuszynski | 041673/2047 | 8867 |

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| EXAMINER | |
|---|---|
| CHEN, SHIN LIN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 04/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/730,790 | TUSZYNSKI ET AL. | |
| | Examiner | Art Unit | |
| | Shin-Lin Chen | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,6,9,10 and 21-46* is/are pending in the application.

4a) Of the above claim(s) *6,9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 21-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-24-05 has been entered.

Applicants' amendment filed 2-24-05 has been entered. Claim 1 has been amended. Claims 2-5, 7, 8 and 11-20 have been canceled. Claims 21-46 have been added. Claims 1, 6, 9, 10 and 21-46 are pending and claims 1 and 21-46 are under consideration.

### *Priority*

Applicants' claiming the benefit of Application No. 09/620,174, filed 7-19-00, now US patent No. 6,683,058, is acknowledged.

Applicants argue the priority of the '053 application (amendment, p. 13, third and forth paragraphs). Examiner is confused with the '053 application applicants talked about. There is no '053 application regarding the benefit of priority.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1 and 21-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for stimulating neuronal growth and activity in insular and inferior temporal cortices, cingulated and frontal cortex, and hippocampus by directly **grafting genetically modified fibroblast cells producing human NGF** into Ch4 cholinergic subdivision of a monkey, wherein the neuronal cells in insular and inferior temporal cortices, cingulated and frontal cortex, and hippocampus are innervated by the Ch4 cell population, does not reasonably provide enablement for a method for ameliorating neuronal atrophy and loss in a mammalian brain by delivering a neurotrophin-encoding transgene composition via various administration routes to preselected delivery sites in the brain for expression of neurotrophin at, or within diffusion distance of, targeted neurons to stimulate non-chemotropic growth in the targeted neurons, or a method for stimulating neuronal growth and activity by delivering a neurotrophin-encoding transgene composition via various administration routes to a region of the brain having targeted neurons and the expressed growth factor stimulates growth of neurons in **another region** of the brain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1, 21-32, 39, 41-43 and 46 are directed to a method for ameliorating neuronal atrophy and loss in a mammalian brain by delivering a neurotrophin-encoding transgene composition to preselected delivery sites in the brain for expression of neurotrophin at, or within diffusion distance of, targeted neurons, such as cholinergic neurons in the cortical region, to stimulate non-chemotropic growth in the targeted neurons. The cortical region of the brain is insular or temporal cortex, frontal, cingulated, entorhinal or hippocampal cotices. Claims 27 and

31 specify the region of the brain containing the argeted neuron is the striatum. Claims 28 and 32 specify the treated mammal is a human with Alzheimer's disease and Parkinson's disease, respectively. Claims 39 and 41-43 specify the transgene encodes NT-3, neurturin, NT-4/5 and perspephin, respectively. Claims 33-38, 40, 44 and 45 are directed to a method for stimulating neuronal growth and activity by delivering a neurotrophin-encoding transgene composition to a region of the brain having targeted neurons and the expressed growth factor stimulates growth of neurons in another region of the brain. Claims 34-36, 44 and 45 specify the transgene composition is delivered directly into the preselected delivery sites. Claims 35, 44 and 45 specify the expression vector is a viral vector, such as adeno-associated viral vector and lentiviral vector. Claim 36 specifies the $10^{10}$ to $10^{12}$ viral particles/ml of composition is delivered. Claims 38 and 40 specify the traasgene encodes NGF and GDNF, respectively.

The specification discloses intraparenchymal delivery of genetically modified fibroblast cells expressing human NGF to monkey brain and shows significant reversal of age-related decline in the regions, including insular and inferior temporal cortices, cingulated and frontal cortex, and hippocampus, that are innervated by the targeted cortical cholinergic Ch4 cell population (e.g. specification, p. 19-20). The claims encompass delivering any growth factor encoding transgene in any vector via various administration routes to preselected delivery sites in a mammalian brain such that therapeutic effect could be obtained to ameliorate neuronal trophy and loss in any distant site of said brain in vivo or to stimulate neuronal growth and activity in any region other than the preselected delivery sites in said mammalian brain in vivo. The targeted neurons in claim 1 can be at the same site of the preselected delivery site, within diffusion distance to the preselected delivery site, or at any distance remote from the preselected

delivery site. Claims 33-38, 40, 44 and 45 encompass stimulating neuronal growth and activity in neurons in any region of the brain other than the region of the brain having targeted neurons.

The specification fails to provide adequate guidance and evidence for how to deliver any growth factor encoding trasngene in any vector to preselected delivery sites in a mammalian brain via various administration routes, such as systemic administration or administration at a site distant from the brain, so as to provide therapeutic effects and to ameliorate neuronal atrophy and loss accompanying normal aging in neurons that are remotely distant from said preselected delivery sites in said mammalian brain *in vivo*. The specification also fails to provide adequate guidance and evidence for how to deliver a neurotrophin-encoding transgene composition to a region of a mammalian brain having targeted neurons so as to stimulate neuronal growth and activity in neurons in any other region in said mammalian brain.

The claims read on gene therapy *in vivo*. Grafting cells secreting NGF into a mammalian brain is different from administering a transgene composition into a mammalian brain. The genetically modified cells secreting NGF already have NGF expressed in said modified cells while said cells are grafted into the mammalian brain, however, a transgene composition encoding a growth factor hasn't yet expressed the growth factor while the transgene composition is delivered to the mammalian brain. The specification only provides the data for grafting genetically modified cells into a mammalian brain and stimulating neuronal growth in the cortical regions that are innervated by the Ch4 cell population, which are the targeted neurons in the region grafted with genetically modified cells.

The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to

desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Verma et al., 1997 (Nature, Vol. 389, pages 239-242) reports that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus, far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (see page 239, right column). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels

and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract). Administration route of a transgene to a subject palys an important role in determining the efficiency of gene transfer in vivo

It also was well known in the art that brain is separated from general circulation by the blood brain barrier. Castro et al., 2001 (Histl. Histopathol., Vol. 16, p. 1225-1238) points out that the brain offers a particular challenge for gene delivery to its constituent cells because it is "made up of mostly non-dividing cells, the skull limits direct injection of vectors into the brain, the blood brain barrier inhibits the easy entry of vectors injected into the bloodstream, and post mitotic target cells restrict what type of vector can be used to deliver genes to the brain" (e.g. abstract). "The main challenges holding back the widespread clinical implementation of neurological gene therapy are technical limitations of current transgene delivery system, i.e. the gene transfer vectors...short term expression of the potentially therapeutic transgenes, coupled to the instability of vectors in the presence of the inflammatory and immune responses directed against the vectors and/or transgenes, reduce the efficiency of delivered therapeutic transgenes...Factors affecting vector stability in target cells/tissues, remain to be identified" (e.g. page 1226, right column).

Although US patent '058 has claims directed to delivering a neurotrophin encoding transgene composition to a mammalian brain to ameliorate the defect, disease or damage, however, Patent '508 has limitation that the transgene is directly delivered to the brain and is expressed in, or within 500 um from, a targeted cell, and no more than about 10 mm from another delivery site. However, the claimed invention of the present application does not have those limitations. The targeted neurons in claims 1, 21-32, 39, 41-43 and 46 can be at the same

site of the preselected delivery site, within diffusion distance to the preselected delivery site, or at any distance remote from the preselected delivery site. The specification fails to provide an enabling disclosure for ameliorating neuronal atrophy and loss in a region of a mammalian brain that is distant, including the region containing neurons that are innervated by the neurons at the delivery sites, from the preselected delivery sites of the transgene composition. The specification fails to provide evidence whether sufficient neurotrophin protein is expressed at the delivery sites and whether sufficient expressed neurotrophin protein can be transport to distant region of the brain so as to ameliorate neuronal atrophy and loss at said distant region. In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to administer any growth factor encoding transgene in any vector to a mammalian brain via various administration routes at preselected delivery sites so as to provide therapeutic effects and to ameliorate neuronal atrophy and loss at a region that is distant from said preselected delivery sites in said mammalian brain *in vivo*.

Further, claims 33-38, 40, 44 and 45 encompass stimulating neuronal growth and activity in neurons in any region of the brain other than the region of the brain having targeted neurons. The specification fails to provide adequate guidance and evidence for delivering a neurotrophin-encoding transgene composition to a region of a mammalian brain, for example, frontal pole, inferior frontal gyrus, or superior frontal gyrus, and stimulating neuronal growth and activity in a region that is remotely distant from the delivery site, such as occipital pole, angulat gyrus, inferior parietal lobule, and superior parietal lobule. The specification fails to provide evidence whether sufficient neurotrophin protein is expressed at the delivery sites and whether sufficient expressed neurotrophin protein can be transport to any distant region of the brain so as to

stimulate neuronal growth and activity at said distant region. As discussed above, grafting cells secreting NGF into a mammalian brain is different from administering a transgene composition into a mammalian brain. The state of gene therapy in vivo was unpredictable at the time of the invention. The fate of the DNA vector itself, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, the protein's compartmentalization within the cell, or its secretory fate, once produced, and the administration route are all important factors for a successful gene therapy in vivo.

For the reasons set forth above, it would have required one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and the level of one of ordinary skill that is high, and the unpredictable nature of the art.

Applicants argue that issued patent '058 confirms that transfection and expression of a transgene at a sufficient level to produce a biological response can be achieved by introducing a growth factor-encoding expression vector into brain tissue. Applicants further argue that the expressed growth factor can be transported intracellularly to distant axonal termini of the nerve via retrograde and anterograde transport or via intercellular transport (e.g. amendment, p. 15-17). This is not found persuasive because of the reason set forth above under 35 U.S.C. 112, first

paragraph, enablement rejection. Although US patent '058 has claims directed to delivering a neurotrophin encoding transgene composition to a mammalian brain to ameliorate the defect, disease or damage, however, Patent '508 has limitation that the transgene is directly delivered to the brain and is expressed in, or within 500 um from, a targeted cell, and no more than about 10 mm from another delivery site. However, the claimed invention of the present application does not have those limitations. The specification fails to provide evidence whether sufficient neurotrophin protein can be expressed at the delivery sites via gene delivery in vivo and whether sufficient expressed neurotrophin protein can be transport to distant region of the brain so as to ameliorate neuronal atrophy and loss at said distant region. The specification fails to provide adequate guidance and evidence for delivering a neurotrophin-encoding transgene composition to a region of a mammalian brain, for example, frontal pole, inferior frontal gyrus, or superior frontal gyrus, and stimulating neuronal growth and activity in a region that is remotely distant from the delivery site, such as occipital pole, angulat gyrus, inferior parietal lobule, and superior parietal lobule. The specification also fails to provide evidence whether sufficient neurotrophin protein is expressed at the delivery sites and whether sufficient expressed neurotrophin protein can be transport to any distant region of the brain so as to stimulate neuronal growth and activity at said distant region. As discussed above, grafting cells secreting NGF into a mammalian brain is different from administering a transgene composition into a mammalian brain. The state of gene therapy in vivo was unpredictable at the time of the invention. The fate of the DNA vector itself, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the

stability of the mRNA produced, the amount and stability of the protein produced, the protein's compartmentalization within the cell, or its secretory fate, once produced, and the administration route are all important factors for a successful gene therapy in vivo.

Applicants argue that the claims should not be limited to administration of an expressible growth factor within 500 um of a targeted neuron and the specification suggests the diffusion of the expressed growth factor can be expected to reach about 500 um from the target site. Applicants further argue that the non-chemotropic effects of axons can deliver growth factor to a farther distance than the concentration diffusion of the growth factor (chemotropic) (e.g. amendment, p. 18-19). This is not found persuasive because of the reason set forth above under 35 U.S.C. 112, first paragraph, enablement rejection and the reasons set forth above in the preceding paragraph.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER